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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/362,598	07/28/99	WEINSTOCK J	3948/79934

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EXAMINER	
SMITH, L	
ART UNIT	**PAPER NUMBER**
1645	16

DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File Copy

Office Action Summary

Application No.	Applicant(s)
09/362,598	Weinstock et al
Examiner	**Group Art Unit**
Lynette R. F. Smith	1645

☒ Responsive to communication(s) filed on *Feb 26, 2001*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *24, 26, and 28-32* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24, 26, and 28-32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The examiner acknowledges the amendment filed 2/26/01. The amendment will be entered and the finality of the last office action has been withdrawn.

3. Upon further consideration by the examiner, all previous rejections are withdrawn.

4. Claims canceled are claims 1-23, 25, 27, 33-35. Claims pending and under consideration are claims 24, 26, 28-32.

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132. The sequence which is not in compliance is found on page 49 of the specification.

OBJECTION TO THE SPECIFICATION

6. The specification is objected to because the amendment submitted 9/12/00 deleted IgG2a from page 22, line 14 and replaced it with IgG2. Page 22 of the instant specification states that in humans IgG2 is generally indicative of a Th1 response, whereas IgG2 is indicative of an

Th2 response. It would appear that IgG2 is not an indicator of differentiation between human Th1 and Th2 responses. This is confusing. Clarification is required.

NEW GROUNDS OF REJECTION

7. Claims 24, 26, 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of determining the immune response of mice to co-infection with M. avium and S. mansoni with and without TNBS treatment and infection of mice with T. muris, with TNBS treatment comprising determining the amounts of IL-4 and IFN-γ, does not reasonably provide enablement for a method of screening an helminthic parasite preparation for one or more components that reduce excessive Th1 immune responses, the preparation prepared by fractionating and sub-fractionating the helminthic preparation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is no guidance in the specification concerning how one would obtain sub-fractions of the homogenate and which sub-fractions would possess the claimed functions. The specification does not disclose how the sub-fractions were obtained and used in the assay or what the molecular weights are of the sub-fractions. The specification does not disclose structure and/or composition of peptides, proteins, lipids, glycolipids, glycoproteins, carbohydrates and/or metabolites used in the claimed method and whether or not these components (which are encompassed by the broad claims) reduced an excessive Th1 immune response. What were the active helminthic homogenate components and subfractions thereof which regulated the immune

response such that one would reasonably know what was encompassed by such components? The specification fails to teach which helminthic fraction or subfraction was able to modulate the immune response because mice were infected only with S. mansoni and M. avium cells (see page 38 of the instant specification) taken from infected mice and re-stimulated in vitro with soluble egg antigen(SEA) and purified protein derivative (PPD). It appears that in order to reduce Th1 excessive responses, mice had to be infected with mycobacterial antigens. It is not clear from the examples that SEA or any helminthic homogenate or preparation reduced any excessive Th1 response as would be required by the broad claims. Examples appearing on pages 40-43 show inhibition of IFN-γ from spleen cells of infected (T. muris and S. mansoni) mice when treated with TNBS. Again there is no showing of a fractionation or a sub-fractionation of helminthic preparations.

The specification does not disclose how one would perform the assay in vivo. What are the parameters or markers one would look for to determine reduction of biological activity? The claims are not limited to in vitro assays and indeed applicant claims an in vivo method. What are the steps involved in the in vivo method of assaying for reduction of Th1 immune responses? In view of the lack of guidance provided by the specification showing sub-fractionation of preparations and how one would assay in vivo, it would require undue experimentation of one of skill in the art to make and use the invention commensurate in scope with the claimed subject matter.

8. Claims 26 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language of the claims is not as precise as the subject matter permits such that one may reasonably know the metes and bounds of the claims. The claims are indefinite because it is unclear in claim 26, where the further steps are to be performed. Are the further steps performed after separating the fractions (i.e. after step c of claim 24) or after assaying the fractions (i.e. step d of claim 24)? Claim 32 is unclear with respect to how one would assay activity in vivo . Clarification is required in order to overcome this rejection.

9. Claims 24, 26, 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Metwali et al, 1996, in view of Boros et al, 1970. The claims are drawn to a method of screening an helminthic preparation for one or more components that reduce an excessive Th1 immune response. The method comprises preparing and fractionating the preparation (i.e. several rounds of fractionation) and assaying the products for their ability to reduce an excessive Th1 immune response.

Metwali et al teach a method of determining the role of IL-4 in regulating the production of IFN-γ and Th1 inflammation in the granulomas from mice infected with *Schistosoma mansoni*. Granuloma cells were assayed for the production of cytokine (IFN-γ, IL-4, IL-5 and IL-10) before and after stimulation with a soluble egg antigen (prepared from schistosome eggs)(abstract, Material and Methods, figures 5 and 6). Metwali et al state that mice infected with schistosomiasis normally develop strong Th2 like granulomas that produce large amounts of IL-4

and IL-5, but only small amounts or quantities of IFN-γ and that IL-4 can inhibit the development of IFN-γ producing T cells (page 4548, second column, 5th paragraph). Additionally, it is known that mice infected with S. mansoni mount a strong type 2 immune response, that the parasite worms living in the portal vein produce ova and the eggs release antigens that induce this strong cytokine (IL-4 and IL-5) response and little IFN-γ (page 4546, second column). This would suggest that there are substances or components in the eggs which reduce Th1 (i.e. IFN-γ) activity. Metwali et al differ from the claimed invention by not specifically describing fractionating the antigen and subjecting the antigen to chromatographic techniques.

Boros et al, teach a method of isolating antigens from Schistosoma mansoni eggs. The method comprises disrupting the mansoni eggs, homogenizing the preparation, separating via centrifugation and further characterizing the antigen via electrophoresis (page 490, figure 1 and pages 497-498). It would have been obvious to one of ordinary skill in the art at the time the invention was made to screen for components, in soluble egg antigens, that reduce excessive Th1 immune responses comprising the steps of preparing the homogenate, fractionating, separating, purifying (via electrophoresis) and assaying the antigen for its ability to reduce excessive Th1 immune responses because Metwali et al teach assaying for cytokines produced from schistosome egg antigen which reduced Th1 responses. It should be noted that Metwali stated that large amounts of Th2 cytokines were produced as opposed to very little Th1 cytokine. It would have been expected, barring evidence to the contrary, that the antigen identified would be pure (and capable of modulating the response) because Boros et al teach techniques which are similar or

obvious or analogous variants of the claimed steps in the method. The criticality of an in vitro or in vivo assay has not been established and would be a matter of design choice.

10. Claims 24, 26, 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pearce et al, (1991) in view of Pearce et al, (1988). The claims are drawn to a method of screening an helminthic preparation for one or more components that reduce an excessive Th1 immune response. The method comprises preparing and fractionating the preparation (i.e. several rounds of fractionation) and assaying the products for their ability to reduce an excessive Th1 immune response.

Pearce et al (1991) teach a method of identifying antigens from the helminthic parasite *Schistosoma mansoni* for the ability to reduce Th1 immune responses (abstract and pages 164-165). The method comprises preparing parasite antigens (e.g. eggs, cercariae, soluble extracts of schistosomula, adult worms and egg)(Materials and Methods, page 160) and screening those preparations for the production of either IFN-γ (Th1 response cytokine) or IL-5 (Th2 response cytokine)(figures 1, 5 and tables 2, 3). The method of Pearce et al (1991) is similar to the claimed method. Pearce et al, 1991, differ from the claimed invention by not specifically teaching a method of preparing an helminthic parasite antigen comprising homogenizing, separating homogenate fractions and identifying sub-fractions for biological activity.

However, Pearce et al, 1988, teach a method of preparing antigens from *Schistosoma mansoni* which comprises obtaining adult schistosomes, homogenizing in phosphate buffered saline, centrifuging and purifying by immunoaffinity chromatography (pages 5678-5679 under

Materials and Methods). It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare schistosome antigens via homogenization and immunoaffinity column chromatography as outlined by Pearce et al, 1988, and assay for components which reduce excessive Th1 responses as outlined by Pearce et al, 1991. It would have been expected, barring evidence to the contrary, that the purified schistosoma antigens would be identified for their capability of reducing excessive Th1 responses because Pearce et al (1991) specifically identify and compare antigens and their abilities to down regulate Th1 cytokine production. The criticality of an in vitro or in vivo assay has not been established and would be a matter of design choice.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Lynette F. Smith whose telephone number is (703) 308-3909. The examiner can normally be reached on Monday-Thursday from 8:00 am to 5:00 pm.

The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

12. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SMITH/lfs
March 27, 2001

L. F. Smith

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